Presentation to the ICD-9-CM Coordination and Maintenance Committee

Dr. MG Blitzer on behalf of the American College of Medical Genetics

12/5/2003

Metabolic Disorders

- Over the last decade, our understanding, diagnostic ability and treatment options for inherited metabolic disease has increased markedly.
- Several groups of potentially treatable disorders identified that are not uncommon:
  - Fatty Acid Oxidation disorders
  - Peroxisomal disorders
  - Mitochondrial disorders

Rationale for New Codes

- New disorders are now recognized that, in aggregate, are not uncommon
  - More frequent than more familiar diseases such as PKU, galactosemia and Tay-Sachs disease.
- There are now specific diagnoses for numerous disorders but no specific codes.
- Many of these disorders are now screened for by newborn testing.

FATTY ACID OXIDATION

- Plays a major role in energy production during periods of fasting
- Does not occur in the brain
- Many different steps involved in metabolic pathway – defects in any of these can result in a metabolic disorder

FATTY OXIDATION DISORDERS (Clinical/Lab Findings)

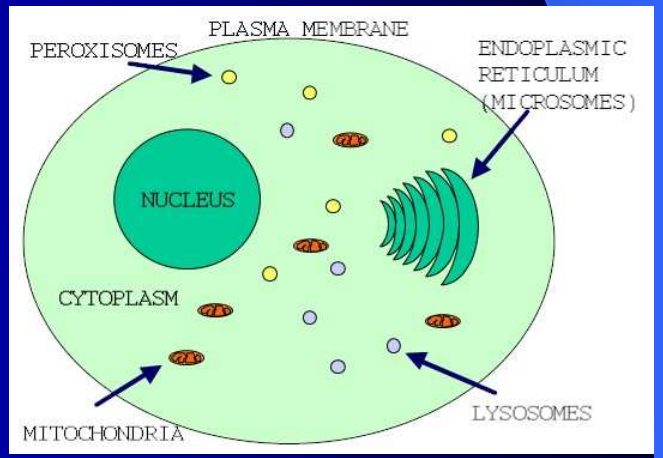
- Typically present at a young age but can occur at any age, including adulthood
- Occurs at least as frequently as PKU
- Following fasting or viral infection, may present with episodes of vomiting, hypotonia, lethargy, hypoglycemia and coma –> life-threatening
- Some disorders result in chronic progressive muscle weakness, cardiomyopathy, or congenital anomalies.

MCADD

- Medium Chain Co-A Acyl-Dehydrogenase Deficiency – Prototype for FAO disorders
- Incidence ~1:15,000 Northern European
- 25-50% first episode fatality rate
- Avoid Prolonged Fasting, ± Carnitine
- Requires new methodology for identification for diagnosis
  - Tandem Mass Spectrometry

PEROXISOMES

- Single membrane organelles within cell
- Both anabolic and catabolic functions
  - Cholesterol and bile acid biosynthesis
  - Metabolism of very long-chain fatty acids
  - H_2O_2 metabolism
- Disorders result from defects in the formation or functioning of peroxisomes



Examples of Peroxisomal Disorders

- **Zellweger syndrome – biogenesis defect**
- **X-linked adrenoleukodystrophy –single protein defect**
  - **“Lorenzo’s Oil”**
- **Rhizomelic chondrodysplasia punctata – skeletal disorder**

Mitochondrial Disorders

- Mitochondria are cellular organelles involved in energy production and utilization
- Have their own DNA; disorders result from defects in mtDNA or nuclear DNA
- Disorders are many and varied
  - Neurological involvement: myopathies and encephalopathies

New Code Recommendations

- Under 277.8 Other specified disorders of metabolism
- **New code: 277.85 Disorders of fatty acid oxidation**
  - Carnitine palmitoyltransferase deficiencies (CPT1,CPT2)
  - Glutaric aciduria type II (type IIA, IIB, IIC)
  - Long chain/very long chain acyl CoA dehydrogenase deficiency (LCAD, VLCAD)
  - Long chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHAD)
  - Medium chain acyl CoA dehydrogenase deficiency (MCAD)
  - Short chain acyl CoA dehydrogenase deficiency (SCAD)

Add Excludes: primary carnitine deficiencies (277.81)

New Code Recommendations

- Under 277.8 Other specified disorders of metabolism
- **New Code: 277.86 Disorders of peroxisomal disorders**
  - Adrenomyeloneuropathy
  - Infantile Refsum disease
  - Neonatal adrenoleukodystrophy
  - Rhizomelic chondrodysplasia punctata
  - X-linked adrenoleukodystrophy
  - Zellweger syndrome

New Code Recommendations

- **New Code: 277.87 Disorders of mitochondrial metabolism**
  - Kearns-Sayre syndrome
  - Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes syndrome (MELAS)
  - Myoclonus with epilepsy and with ragged red fibers syndrome (MERFF)
  - Mitochondrial neurogastrointestinal encephalopathy (MNGIE)_
  - Neuropathy, ataxia and retinitis pigmentosa syndrome (MARP)

Add Excludes: disorders of pyruvate metabolism (271.8)
Leber's disease (377.16)
Leigh's encephalopathy (330.8)
Reye's syndrome (331.81)

Autosomal Deletion Syndromes

- Autosomal: involves one of the numbered (ie, non-sex chromosomes)
- Deletion: an abnormality of DNA that involves missing material. These can range from very small (as little as 1 base pair) to very large (involving millions of base pairs of DNA)

Autosomal Deletion Syndromes

- Recommendations for ICD-9-CM
  - Remove antimongolism (this is archaic and pejorative term, not clinically relevant)
  - Add subcodes within 758.3
    - 758.31 Cri-du-Chat (currently listed under 758.3)
    - 758.32 Velo-Cardio-Facial Syndrome
    - 758.33 Other microdeletions (with Smith-Magenis syndrome and Miller-Dieker syndrome listed)
    - 758.39 Other autosomal deletions

Cri-du-Chat syndrome

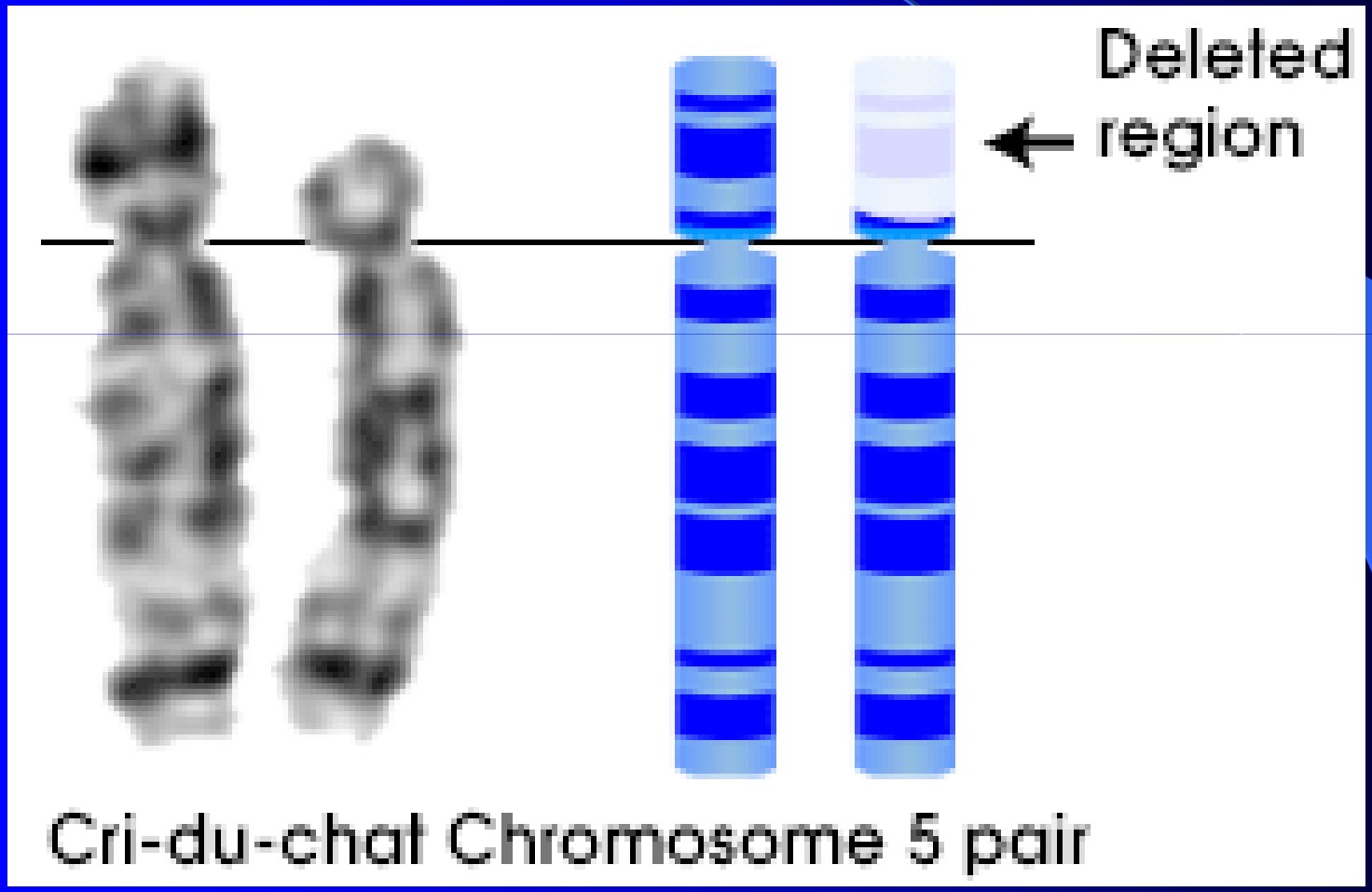
- First recognized syndrome due to a deletion (1963)
- Involves a missing piece of the short arm of chromosome 5 (5p-)
- Only deletion syndrome currently listed in ICD-9-CM

Cri-du-Chat syndrome

- Mental retardation
- Microcephaly
- Round face
- Congenital Malformations
- Laryngeal anomaly leading to cry sounding like cat (infants)

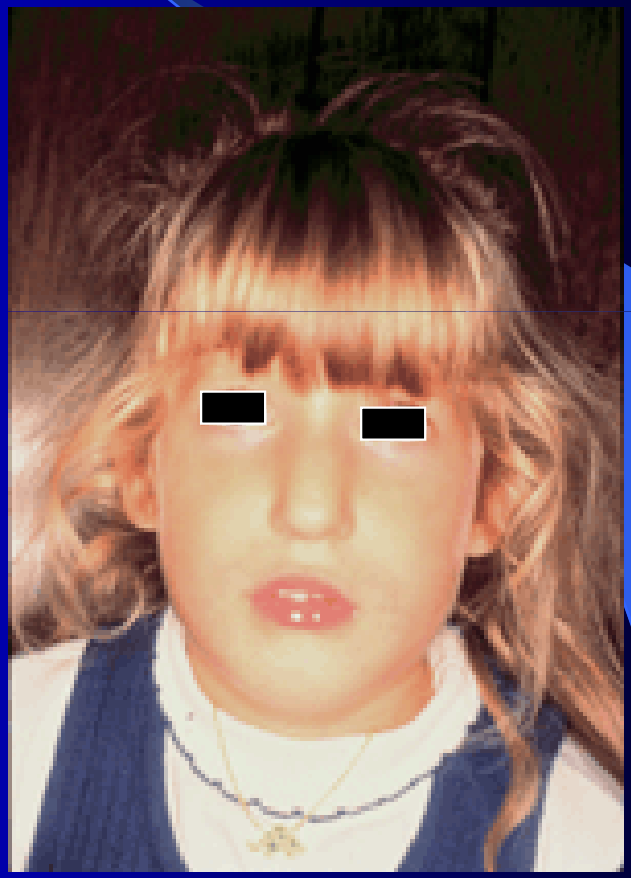
Picture from Cri-du-Chat Syndrome Website

Cri-du-Chat syndrome



Velo-Cardio-Facial Syndrome

- Abnormalities of palate including clefts (velo)
- Cardiac malformations (frequently septal defects)
- Unusual facial features
  - Long face
  - Flattened cheeks
  - Dark circles under eyes
  - Prominent nose



Velo-Cardio-Facial Syndrome
Other Features

- Learning disabilities/Mental retardation
- Long slender fingers
- Neuropsychiatric abnormalities
- Can be associated with DiGeorge sequence (T-cell immune deficiency, hypercalcemia)
- Caused by deletion 22q11.2

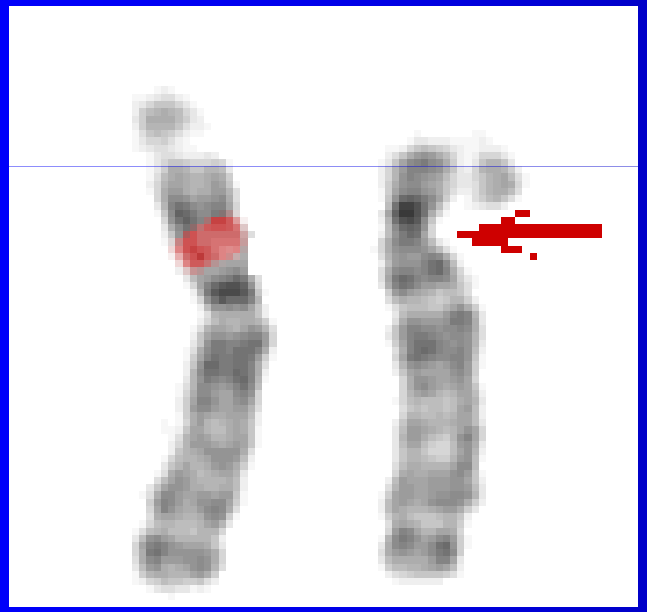
Velo-cardio-facial Syndrome
Rationale for Including in ICD 9-CM

- Most common autosomal deletion syndrome (incidence in US ~1:3,000.
  - Compare to Cri-du-chat 1:20-50,000)
- Nearly 100,000 affected in U.S.
- Well recognized syndrome diagnosed by geneticists, cardiologists, otolaryngologists
- Significant number diagnosed in adulthood

Deletion vs. Microdeletion

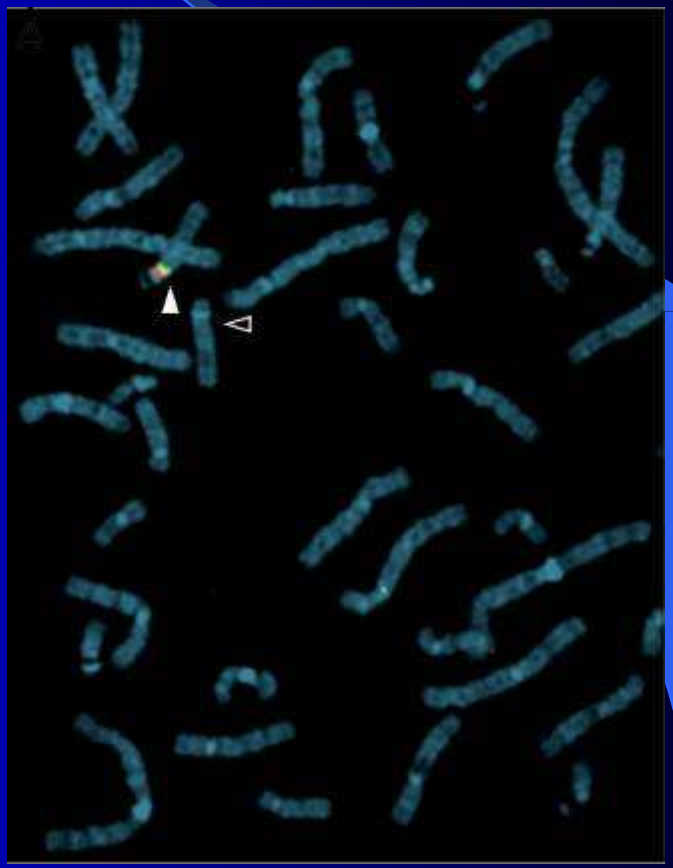
- Deletion visible by standard cytogenetic techniques
- By definition is large (must be a minimum of 1-2 million bases to be visible)
- Usually severe birth defects, mental retardation and frequently shortened life
- Deletion requires special molecular techniques to detect
- Increasingly recognized as cause of specific syndromes
- As a whole are more common than visible deletions

Example:
Prader-Willi Syndrome



Visible deletion

Chromosome 15



Microdeletion (absence of a FISH signal)

Rationale for Separate Code

- Microdeletions are more common than visible deletions
- As more is learned and techniques are improving, more syndromes are found to be due to these microdeletions
- Specific molecular techniques are necessary to diagnose (specific code supports medical necessity for doing additional testing)
- Other conditions due to microdeletions can be added to index (Wolf-Hirschhorn, Jacobsen, etc)

Routine Neonatal Screening

- Began in the 1960's with PKU screening
- Is now expanding to include many metabolic conditions
- Is designed to maximize detection, therefore results in false positives

Rationale for New Code for Neonatal Screening

- Currently physicians are using disease codes for positive screens.
- Therefore, surveillance data are skewed.
- A new code would accurately describe the clinical situation between positive screen and final diagnosis.
- This is analogous to 796.5, “Abnormal finding on antenatal screening.”

New Code Recommendation for Neonatal Screening

- Position new code under 796:
  Other nonspecific abnormal findings
- 796.6 “Nonspecific abnormal findings on neonatal screening”
  - Excludes: nonspecific serologic evidence of HIV